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CENTRAL LABORATORY OF THE RESEARCH COUNCILS
RUTHERFORD APPLETON LABORATORY
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DIDCOT
OXFORDSHIRE OX11 0QX

Patents ADP number *(if you know it)*

6877609003

If the applicant is a corporate body, give the country/state of its incorporation

UNITED KINGDOM

4. Title of the invention

METHOD AND APPARATUS FOR DETERMINING MOLECULAR CRYSTAL STRUCTURES

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

STEVENS, HEWLETT & PERKINS
1 SERJEANT'S INN
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LONDON EC4Y 1LL

Patents ADP number *(if you know it)*

1545003

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Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

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Signature Stevens, Hewlett & Perkins Date 31.7.97

STEVENS, HEWLETT & PERKINS

12. Name and daytime telephone number of person to contact in the United Kingdom SARAH PERKINS 0171 936 2499

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METHOD AND APPARATUS FOR DETERMINING MOLECULAR CRYSTAL STRUCTURES

The present invention provides a method and apparatus for determining molecular crystal structures. In particular, but not exclusively, with the present invention the molecular crystal structure of large organic molecules, such as pharmaceutical compounds, can be determined using data from powder diffraction analysis.

Information on the molecular crystal structure of a molecule is usually obtained through irradiation of a single crystal of the molecule with neutrons or X-rays. Subsequent analysis of the resultant diffraction pattern, which consists of a series of angularly spaced intensity peaks with each peak representing an individual Bragg reflection, provides information on the structure. Whilst this single crystal diffraction technique is an effective technique for determining the crystal structure of a molecule, it can often prove difficult to grow the single crystals necessary for the analysis. Moreover, where the molecule can crystallise in more than one polymorphic form, it is sometimes the case that it can prove very difficult to grow a single crystal of a particular polymorph.

To address these problems, a powder diffraction analysis was developed in which a crystalline powder of the material under analysis is irradiated instead of a single crystal. Analysis of the resultant diffraction pattern is hampered by the fact that the diffraction pattern may include Bragg reflections that partially or fully overlap one another, making it difficult for individual reflections to be identified, and their associated intensities quantified. An example of experimental data from irradiation of a powder sample of the drug substance cimetidine in the form of a graph representing intensity of the Bragg reflections with respect to angular position is shown in Figure 1. This diffraction pattern can be used in a point-to-point comparison with diffraction data calculated from a postulated model of the crystal structure. If there is good agreement between the measured and calculated diffraction data, it may be assumed that the

postulated structure is close to the true crystal structure of the molecule. In general, good agreement is only obtained when there is significant prior knowledge of the true crystal structure of the molecule, as there is an infinite number of crystal structures that may be postulated and compared to the experimental data.

The present invention seeks to address the problems discussed above with respect to existing diffraction analysis techniques and seeks to provide a method and apparatus for determining molecular crystal structures which employs irradiation of crystalline powders and permits analysis without the need for prior knowledge of the approximate crystal structure.

The present invention provides a method for determining molecular crystal structures comprising the steps of: determining from powder diffraction data for the molecule under examination a unit cell and a space group; generating a reduced representation of the powder diffraction pattern, in which the total quantity of diffraction data is significantly reduced whilst maintaining the characteristics of the diffraction data that are representative of the crystal structure under examination; defining the molecular structure in terms of a plurality of internal co-ordinates; determining a set of variables for describing trial molecular structures, derived from said internal co-ordinates and said space group; assigning values to said variables thereby creating a population of trial structures each defined by a unique set of values for said variables; calculating a fitness for each trial structure with respect to the reduced representation of the powder diffraction pattern; determining whether any one of the calculated fitnesses is less than or equal to a predetermined threshold; where none of the calculated fitnesses is less than or equal to the threshold value, selecting at least one survivor from the population of trial structures, altering the values of the variables of at least one of the survivors in accordance with one or more predetermined rules, calculating the fitnesses of the new trial structures; and repeating the steps of selecting survivors, altering the values of the variables and calculating the

fitnesses of the new trial structures until at least one of the calculated fitnesses is less than or equal to the threshold value, and where at least one of the calculated fitnesses is less than or equal to the threshold, outputting the at least one trial molecular crystal structures represented by the successful sets of values.

In a further aspect the present invention provides apparatus for determining molecular crystal structures comprising a structure factor analyser for generating from experimental powder diffraction data for the molecule under examination a unit cell, a space group and a reduced representation of the powder diffraction pattern in which the total quantity of diffraction data is significantly reduced whilst the characteristics of the diffraction data representative of the crystal structure under examination are maintained; a co-ordinate generator for defining the molecule in terms of a set of internal co-ordinates; a controller for determining a set of variables for describing trial molecular structures, derived from said internal co-ordinates and said space group; a searching processor for creating a population of trial structures each defined by a unique set of values for said variables said searching processor including a fitness analyser for calculating a fitness for each trial structure with respect to the reduced representation of the powder diffraction pattern, a thresholding device for determining whether any one of the calculated fitnesses is less than or equal to a predetermined threshold, a survivor selector for selecting at least one survivor from the population of trial structures, a variable adjustment device for altering the values of the variables of at least one of the survivors and output means for outputting the one or more trial molecular crystal structures having calculated fitnesses less than or equal to the threshold value.

Ideally, the reduced representation is in the form of a structure factor intensity listing and associated covariance matrix. Moreover, preferably, the fitness χ^2 of each of the trial structures is determined using the following function:

$$\chi^2 = \Sigma_h \Sigma_k \{ (I_h - c|F_h|^2) (V^{-1})_{hk} (I_k - c|F_k|^2) \}$$

where:

$I_{h,k}$ = extracted intensity from the first analyser

V_{hk} = covariance matrix from the first analyser

c = a scale factor

$F_{h,k}$ = calculated structure factor from trial structure

The search for a three dimensional structure of a molecule which would produce a powder diffraction pattern nearly identical to available experimental results is greatly simplified with the present invention. This is achieved by reduction of trial molecular crystal structures to a unique set of variables and by reduction of the experimental powder diffraction data to a reduced representation such as a structure factor intensity listing which is then used in determining a fitness of the trial structure with respect to the reduced experimental data. The present invention relies on the fact that at its most basic, a molecular crystal structure can be represented by a set of internal co-ordinates describing the molecule under investigation, together with co-ordinates describing the location and orientation of the molecule within a unit cell. The reduction of the molecular crystal structure to a set of variables enables analysis of the trial structures to be performed much more quickly than an analysis performed using the conventional method of describing the crystal structure in terms of the fractional or Cartesian co-ordinates of every atom in the asymmetric unit of the structure. Such conventional representations are considered to be unworkable in a model building sense because of the computing power necessary to position individual atoms independently of each other. The representation of the trial structures used in the invention along with the novel fitness function means that analyses can be performed in seconds or minutes on the current generation of conventional personal computers or workstations. Moreover, the representation is versatile as it allows the invention to work with flexible molecules as well as multiple fragments.

An embodiment of the present invention will now be described by way of example with reference to the accompanying drawings, in which:

Figure 1 is a graph of experimental data from x-ray powder diffraction analysis of cimetidine showing 315 reflections, using an irradiation wavelength of 1.5285Å and a data range for 2θ of 8°-56°;

Figure 2 is a schematic representation of the 2D molecular structure of cimetidine;

Figure 3 is a flow diagram of the method steps for determining a molecular structure in accordance with the present invention;

Figure 4 is a diagram of the crystal structure of cimetidine;

Figures 5a, 5b, 5c and 5d are diagrams showing the progressive development of a trial crystal structure for cimetidine, employing the method and apparatus in accordance with the present invention, overlying the diagram of Figure 4;

Figure 6 is a graph showing the fitness of a trial crystal structure for cimetidine with respect to generations, employing the method and apparatus in accordance with the present invention; and

Figures 7a, 7b and 7c show the molecular structure of dopamine deuterobromide, a graph of the development of a trial structure for the crystal and a diagram of the solution respectively, employing the method and apparatus of the present invention.

The present invention will be described with reference to an experimental determination of the crystal structure of the molecule cimetidine, a histamine H_2 antagonist used in the treatment of stomach ulcers, for which a full single crystal structure (monoclinic Form A) determination has already been performed. Figure 2 shows the 2D chemical formula of the cimetidine molecule, whilst the known arrangement of the cimetidine molecules within the unit cell of the crystal structure is shown in Figure 4.

To determine the molecular crystal structure of cimetidine employing the method and apparatus of the present invention with reference to Figure 3, initially a conventional powder diffraction pattern (10) is obtained from a

crystalline powder sample of cimetidine. The resultant diffraction pattern is shown in Figure 1. The experimental diffraction data (10) is input into a cell dimension analyser (12). The cell dimension analyser (12) uses conventional techniques to assess the diffraction pattern in order to determine the unit cell dimensions of the crystal structure. The diffraction pattern is also input to a structure factor analyser (14) that also receives the unit cell dimensions determined by the analyser (12). The structure factor analyser (14) analyses the experimental diffraction pattern using the lowest symmetry space group consistent with the crystal class determined by the cell dimension analyser (12), reducing the data to a first structure factor intensity listing and an associated covariance matrix. From this listing, the true space group (16) of the crystal structure is determined and used by the structure factor analyser (14) to generate a second structure factor intensity listing and associated covariance matrix (18). By generating this second structure factor intensity listing and associated covariance matrix (18), the total quantity of the original experimental diffraction data is significantly reduced in amount without loss of those characteristics of the data representative of the crystal structure under examination. Thus, the experimental diffraction data is not presented for analysis as a point-by-point profile, but rather in a reduced data form enabling the data to be analysed using a fitness function described in greater detail below.

Using the known 2D chemical formula for cimetidine (20), a co-ordinate generator (22) determines a set of internal co-ordinates (24) which completely describe the three dimensional structure of the molecule. The internal co-ordinates (24) include known data using tabulated bond lengths, bond angles and rigid torsion angles, where necessary, along with identification of unknown variables such as flexible torsion angles. When postulated values for the unknown variables are added, sufficient information is present in the internal co-ordinates to define the conformation of an isolated theoretical cimetidine molecule.

Preferably, the only unknown factors and so the only variables to be

found in the internal co-ordinates are the values of the variable torsion angles (represented by variables τ_1, τ_2, τ_3, τ_4, τ_5...). It is not essential for the bond lengths and bond angles to be held fixed and where appropriate these factors too may be varied in determining the crystal structure of the molecule. It has been found though that variation of the bond lengths and bond angles within chemically sensible bounds has a much smaller effect on the calculated diffraction data than variation of the flexible torsion angles within the structure. Thus for most purposes, acceptable results can be achieved with these factors held fixed.

The output (24) of the co-ordinate generator (22) is supplied to a controller (26) that is also connected to the space group output (16) of the structure factor analyser (14). The controller (26) also includes an input (28) to enable manual setting of selected operational parameters such as the number of trial structures to be analysed in each generation, i.e. the population size. The controller (26) uses the internal co-ordinates and the space group to determine additional variables representing the location and orientation of a molecular structure in the unit cell. Preferably, the location of the structure within the unit cell is defined using a single reference point in fractional co-ordinate space represented by external co-ordinates or variables (x, y, z). The orientation of the molecule at that point may be described using Euler angles (α, β, γ). Alternatively, the orientation of the molecule may be described using a quaternion, q.

In this way the molecular crystal structure is reduced to a set of variables consisting of internal and external co-ordinates:

$\{x, y, z, \alpha, \beta, \gamma, \tau_1, \tau_2, \tau_3, \tau_4, \tau_5...\}$ or $\{x, y, z, q, \tau_1, \tau_2, \tau_3, \tau_4, \tau_5...\}$.

These variables are suitable for iterative mathematical processing and are more amenable to search procedures than the full complement of individual atomic co-ordinates used in conventional techniques.

The output (30) from the controller (26) is then supplied to an iterative searching processor (32). The output (30) consists of the set of variables determined by the controller (26); the complete internal co-ordinates produced by the co-ordinate generator (22); operating

parameters such as the selected size of the population to be employed in the searching procedure; any rules restricting or controlling the values which can be allocated to each of the variables; and any rules controlling the selection of survivors, the breeding and the mutation of survivors, described in greater detail below.

In the method shown in Figure 3, the iterative searching processor (32) employs a genetic algorithm to determine the correct molecular crystal structure. The above mentioned set of variables {x, y, z, α, β, γ, τ_1, τ_2, τ_3, τ_4, τ_5 ...} or {x, y, z, q, τ_1, τ_2, τ_3, τ_4, τ_5 ...} are thus equated to chromosomes, with each individual variable equating to a gene. The genetic algorithm establishes certain protocols based on the concept of 'survival of the fittest', with respect to the selection of survivors, the breeding and the mutation of survivors.

Firstly, within the searching processor (32) an initial population of chromosomes is created (33) by assigning random numbers to each of the genes of each of the chromosomes. The allowable random numbers for any particular gene may be restricted in accordance with rules input from the controller (26). The selected size of this initial population depends somewhat upon the complexity of the structure under investigation, with larger population sizes typically being required for problems involving more variables. In the case of cimetidine, where seven torsion angles were allowed to vary, resulting in thirteen degrees of freedom, a population size of 150 was chosen. The fractional co-ordinates (x, y, z) and Euler angles are randomly set as real numbers normally bounded by the Euclidian normalisers of the space group. The variable torsion angles (τ) are typically randomly set as real numbers in the range 0°-360°.

Using the internal co-ordinates a three dimensional structure of the trial molecule is constructed (35) for each parent in Cartesian space, and then in fractional space with respect to the crystal unit cell. Diffraction data is then determined (37) for each of the trial molecular structures and a fitness value, χ^2, is calculated (39) for each trial structure with respect to

the structure factor intensity listing and covariance matrix. The preferred fitness function employed is as follows:

$$\chi^2 = \Sigma_h \Sigma_k \{ (I_h - c|F_h|^2) (V^{-1})_{hk} (I_k - c|F_k|^2) \}$$

where:

$I_{h,k}$ = extracted intensity from the first analyser

V_{hk} = covariance matrix from the first analyser

c = a scale factor

$F_{h,k}$ = calculated structure factor from trial structure

The fitness values for each of the chromosomes is compared to a predetermined threshold value (41) so that in the event any one of the chromosomes is less than or equal to the threshold value a solution for the molecular structure is output (43). In the event that the fitness values of all of the chromosomes exceed the threshold value, the chromosomes are then supplied (45) to a survivor selector (47). At the same time a counter (49) is increased by one so that a record of the number of generations created is maintained.

Using the fitness values obtained for each of the chromosomes, the survivor selector (47) employs a proportional selection scheme, in which the chances of a chromosome surviving are proportional to its fitness, to select a number of survivors. Other criteria for selecting survivors may alternatively be used. For example, a tournament selection may be employed in which case two chromosomes are selected at random and compared with one another, with the fittest surviving. In particular the Boltzmann tournament may be used as it introduces an element of simulated annealing to the selection process. In addition, the selection may be elitist with the best member of the population in terms of fitness always surviving to enter the next generation.

Additional fitness functions may also be employed instead of, or in combination with the aforementioned fitness function, to further enhance

the analysis of the trial structures. For example, simultaneous fitting of both X-ray and neutron diffraction data; use of a molecular packing function; use of an isolated molecule Lennard-Jones type calculation; use of a rotation / translation function; and use of phase information derived from direct / Patterson methods.

Although the above method is described in terms of the entire population being subject to a common selection, the population may be divided into sub-populations in which each sub-population evolves independently of the other sub-populations albeit that migration from one sub-population to another can be enabled.

The surviving chromosomes are then used to create offspring (51) by allowing the chromosomes to 'breed'. For example, individual genes from different chromosome survivors may be mixed and/or one or more of the genes in a chromosome survivor or its offspring may be mutated by random selection of a new value for the gene. Often, the population size is kept constant throughout this breeding process. The three dimensional structure of each of the offspring is then determined (35), as before, and theoretical diffraction data calculated (37).

The fitness (χ^2) is then evaluated (39) for each of the offspring and the fitness results compared (41) to the predetermined threshold value to determine whether a likely crystal structure for the molecule has been identified. If one of the offspring chromosomes has a fitness value which is less than or equal to the threshold value, or if a predetermined maximum number of generations has been reached, then the search procedure is stopped (43). On the other hand, if the fitness functions of the chromosome offspring all exceed the threshold value and the counted number of generations is less than the maximum allowed number, then the offspring are returned for the selection of survivors (47) and for the creation of new offspring (51).

Additional rules may also be employed where appropriate to constrain the allowable values for the variables. These rules are determined by the controller (26) that may utilise data on crystal fragments

stored in a memory (53). For example, the controller (26) may search through stored crystallographic databases of known crystal structure fragments related to the molecule to provide prior information about torsion angle values likely to be adopted by the structure. Such information can then be implemented either as hard limits on the allowable values the torsion angles may adopt, or as probability distributions for the torsion angles. Furthermore, fragments of the molecule may be located using Patterson methods or direct methods. For example, the location of a heavy atom may be used to anchor a molecule during the analysis by the searching processor (32). This effectively reduces the dimensionality of the problem by three as the fractional reference co-ordinates are then known.

Operation of the processor (32) in the search for the correct 3D molecular crystal structure is thus an iterative procedure with the average fitness for each generation gradually tending towards the global minimum in fitness function space. In Figure 5a, a trial cimetidine crystal structure, corresponding to a chromosome in the first generation initialised at random by the processor (32), is shown overlying the true crystal structure first shown in Figure 3. Figure 5b then shows one of the early offspring determined by the processor having a fitness value of χ^2=980, again overlying the true crystal structure of cimetidine. In Figure 5c, a later offspring having a fitness value of χ^2=430 is shown and the improvement in correspondence between the trial crystal structure and the actual crystal structure is immediately evident. At this point, the crystal structure could be refined using a conventional constrained Rietveld refinement. Hence, the processor (32) may be arranged so that the threshold value for the fitness function is set at around 450. This would result in the search procedure being stopped once the trial structure shown in Figure 5c had been generated, thereby enabling alternative methods to be used to refine the fine details of the trial structure. The advantage of stopping the search procedure at this point is that, usually, conventional methods will be able to refine the fine details of the structure more efficiently than the presently

described method and apparatus.

Continuing with the present method, in Figure 5d an offspring having a fitness value of χ^2=110 is shown at which point the detail of the trial structure is easily refinable. Figure 6 is a graph of trial results for cimetidine using the method described above showing the fitness value of offspring with respect to the number of generations for both average fitness and the best fitness. As can be seen, a refinable structure is obtained within a few hundred generations, and an easily refinable structure is obtained around 3000 generations. This latter structure corresponds to an elapsed time of approximate 40 minutes, with the processor running on a single 175MHz R10000 Silicon Graphics™ workstation.

As further examples for the speed of this method, easily refinable structures for pyrene were determined in around 33 seconds, around 15 seconds for chlorothiazide and 36 minutes for Ibuprofen, with all calculations being performed on a single 200MHz Pentium Pro™ personal computer.

The above method and apparatus may also be used with molecular structures consisting of more than one fragment. As shown in Figures 7a, 7b and 7c an easily refinable structure solution for dopamine deuterobromide using neutron powder diffraction data was achieved in around only 4000 generations. This structure involves not only a dopamine cation, but also a separate bromide anion. Using the present method and apparatus the location, orientation and conformation of the cation, and the location of the anion can be determined simultaneously.

Whilst in the examples given above the individual genes are real numbers, they could equally be represented by binary strings or integer approximations with appropriate scaling factors. Also, in the example given above the experimental diffraction data is reduced to a structure factor listing and associated covariance matrix, it will be apparent that alternative ways of reducing the total quantity of diffraction data may be employed in which the characteristics of the crystal structure under examination are not lost.

In the above example a genetic algorithm searching processor is employed to perform an iterative selection of candidate molecular crystal structures. Alternative iterative analysis processes such as simulated annealing, evolutionary strategies and neural network analysis may be used instead of the genetic algorithm. For example, using a simulated annealing process, the same variables that were treated as genes by the genetic algorithm are individually adjusted by a small perturbation of their current values. If the function value (χ^2 as defined previously) is better than before, then the new values of the variables are retained. If the function value is worse, then the new values of the variables are not automatically rejected. Instead the new values may be retained if allowed by the temperature dependent Boltzmann selection protocol. In this way, 'uphill' (in terms of χ^2) adjustment of the variables is permissible, helping the algorithm to escape from local minima. The initial choice of the temperature is usually high to allow large 'uphill' moves if necessary, but the temperature is usually lowered in some predetermined fashion during the iterative process. Alternatively, the population of the trial structures may be set to one and a Monte Carlo procedure followed.

With the method and apparatus described above, molecular crystal structures may be solved from powder diffraction data alone. Definition of the molecular fragments in terms of internal co-ordinates means that for a single molecular fragment, problem complexity scales with the number of variable torsion angles rather than with the number of atoms in the fragment. Thus, complex structures can be represented by quite short chromosomes and solved relatively easily. The simple description of molecular geometry employed, together with the genetic algorithm analysis and the specified fitness function has thus been shown to be particularly powerful in determining crystal structures from powder diffraction data in a relatively short time frame.

To assist in an understanding of the invention, the method has been described with reference to functional, i.e. analyser/processor units. It will of course be apparent that in practice the method is implemented as a

program on a computer. Indeed, one of the advantages of this method is that the program can be implemented on a number of different computer architectures, including personal computers and a network of personal computers/workstations acting as a parallel computer.

5

Fig 1.

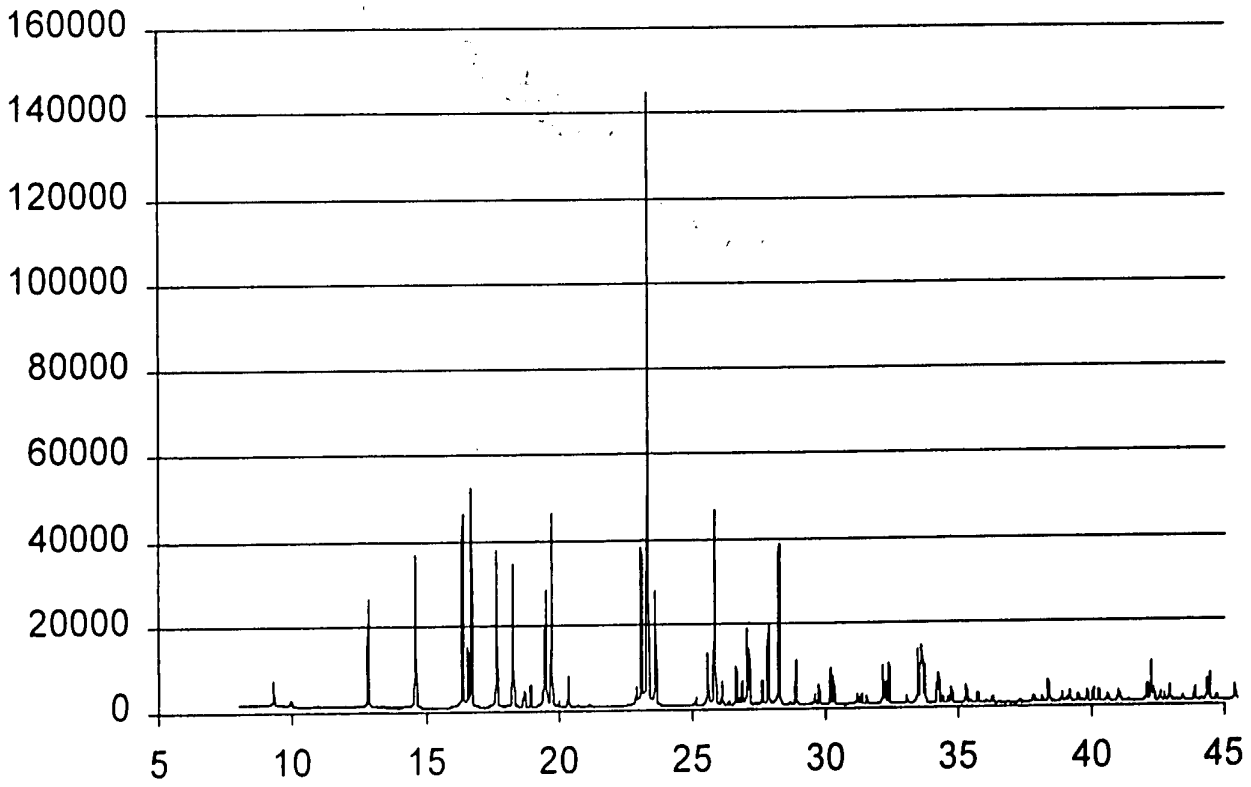
160000
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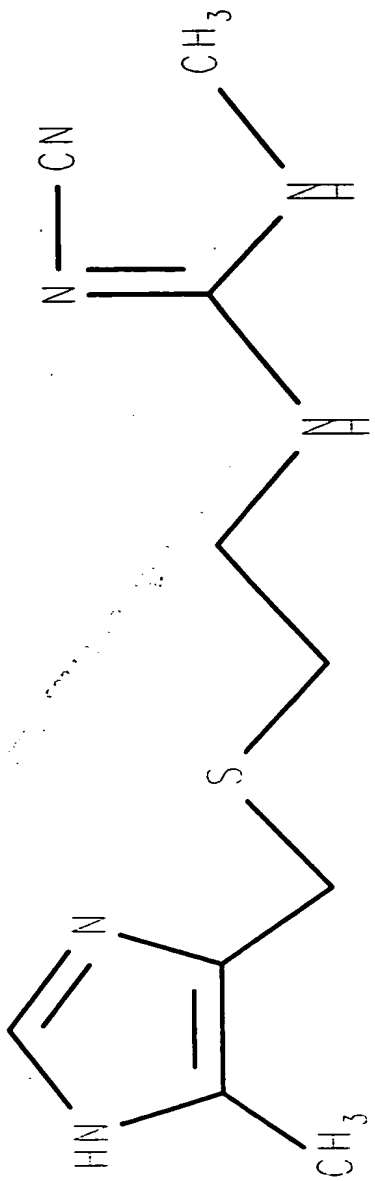
Fig 2.



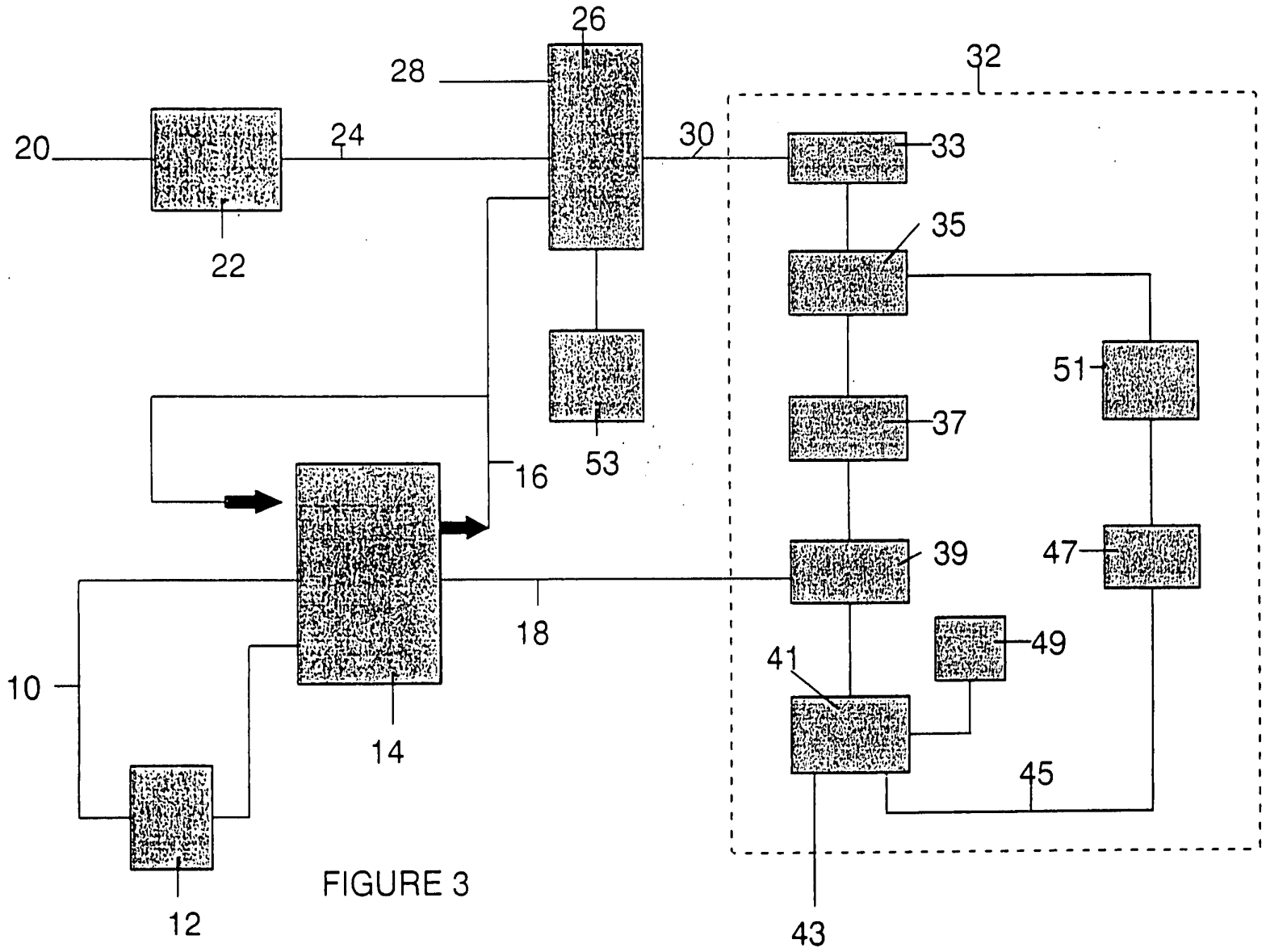


FIGURE 3

Fig 4.

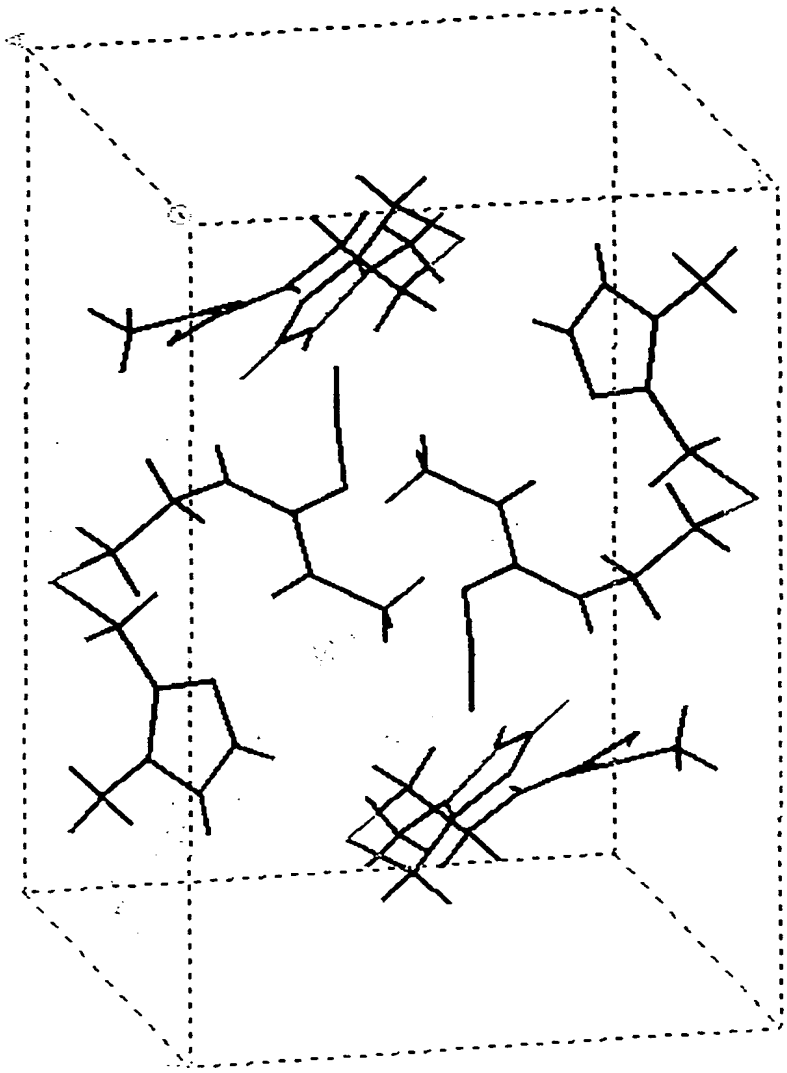


Fig 5a.

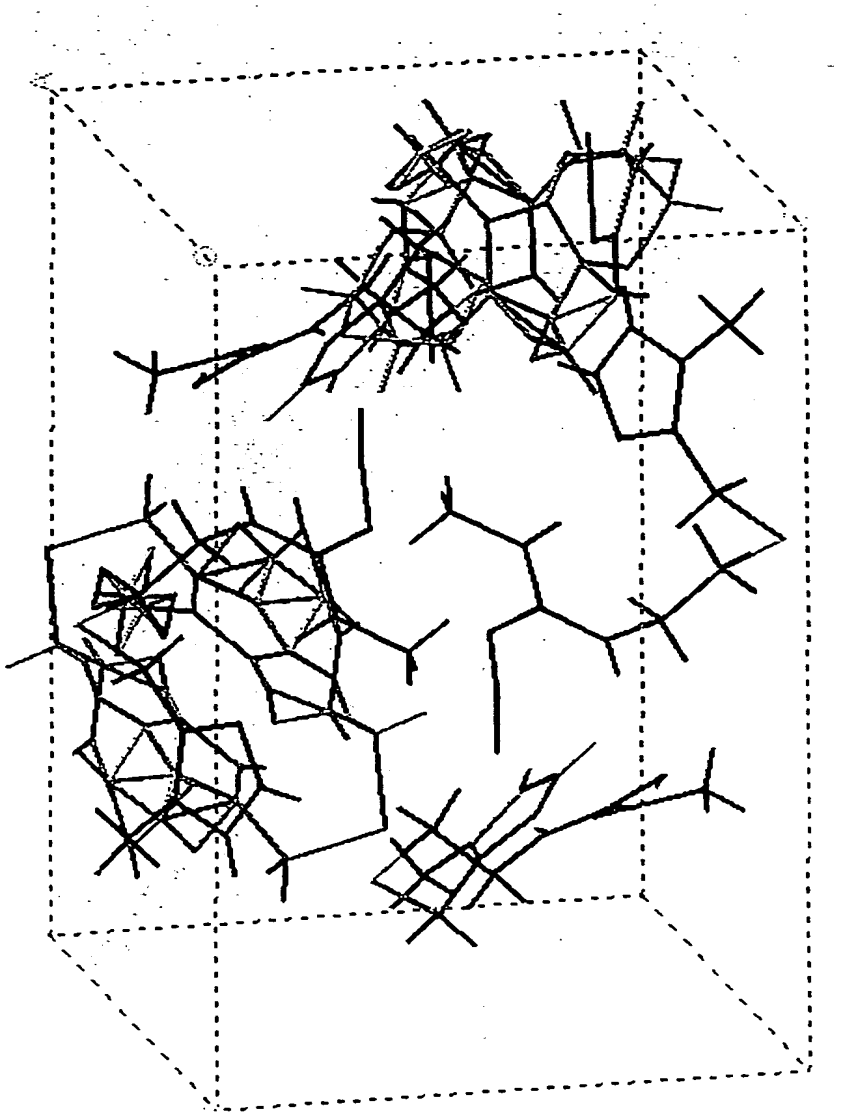


Fig 5b.

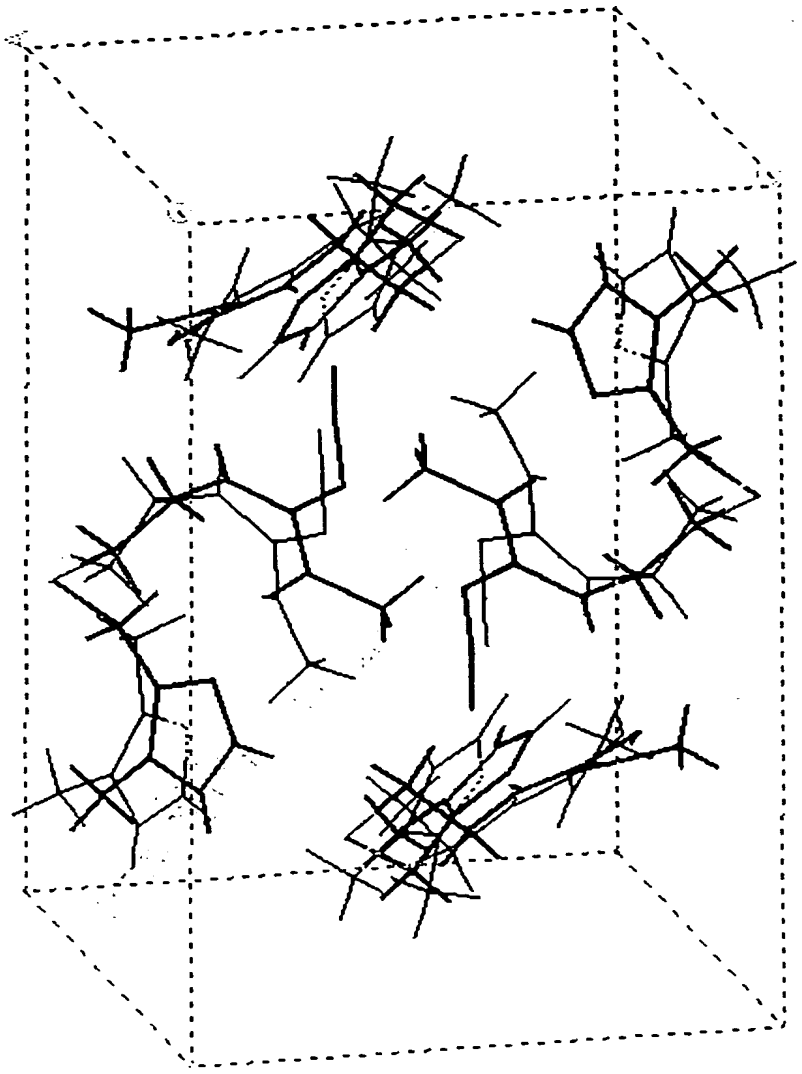


Fig 5c.

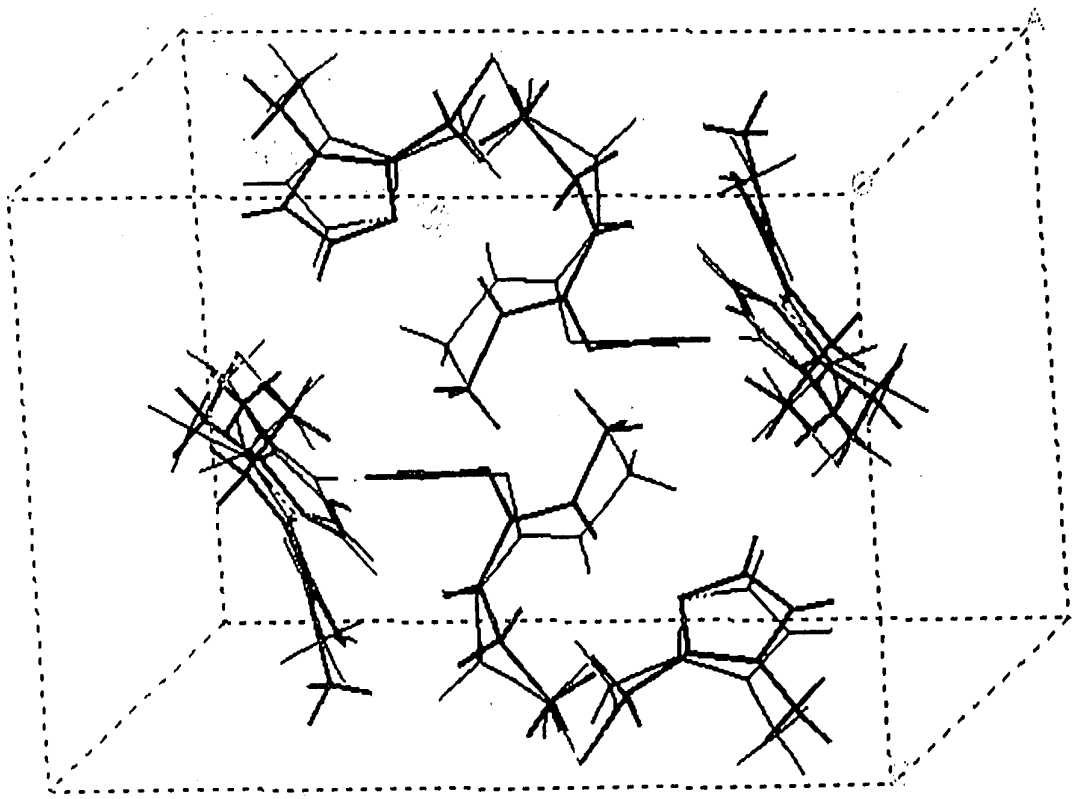


Fig 5d.

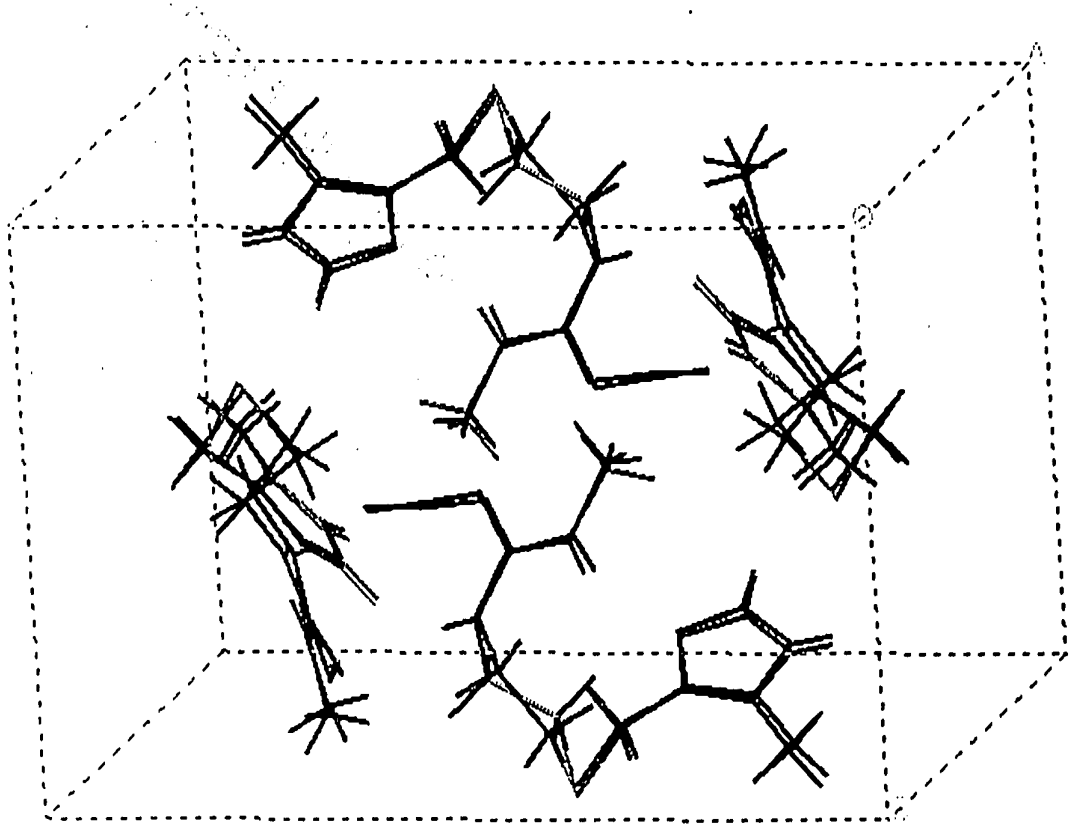


Fig 6.

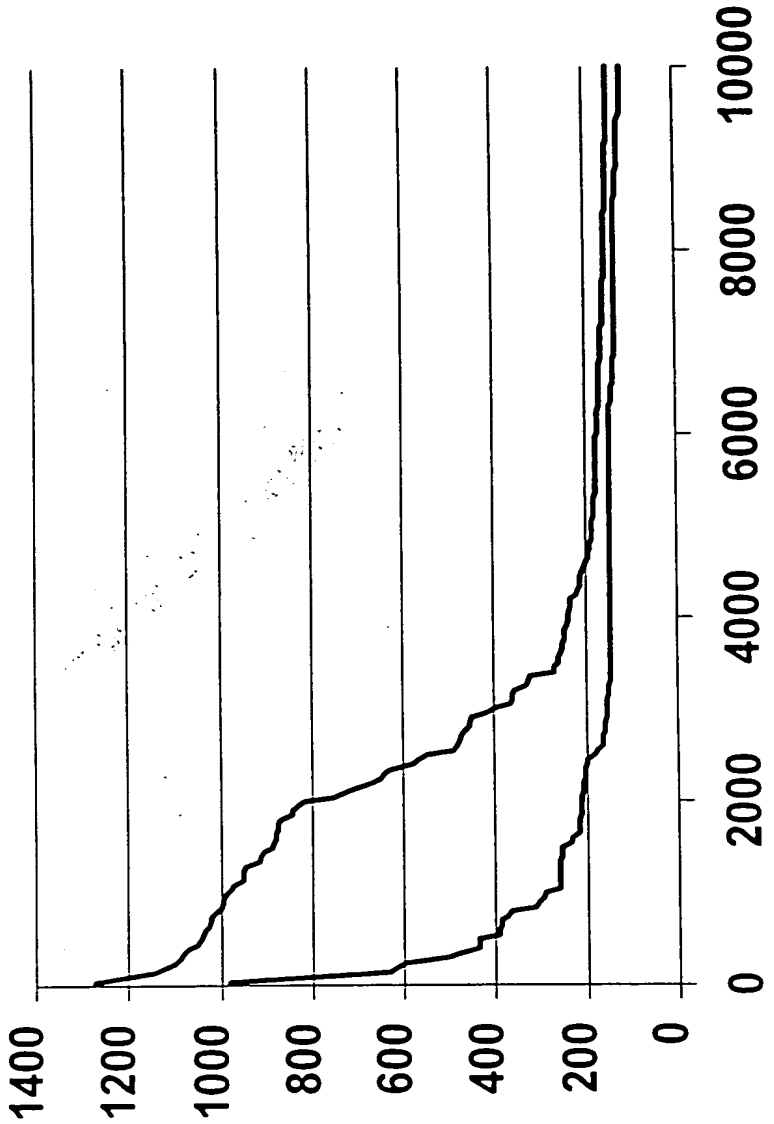


Fig 7a.

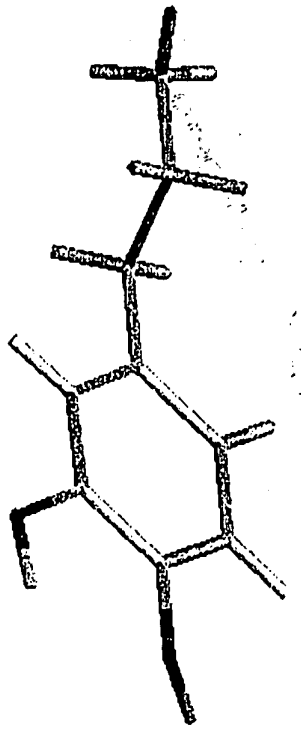


Fig 7b.

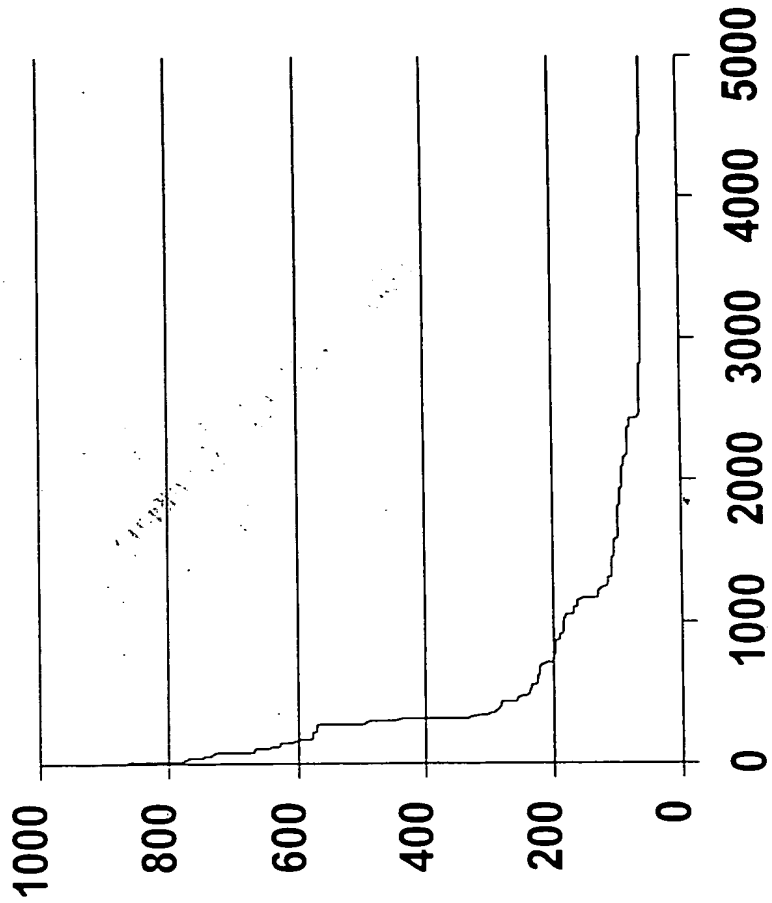
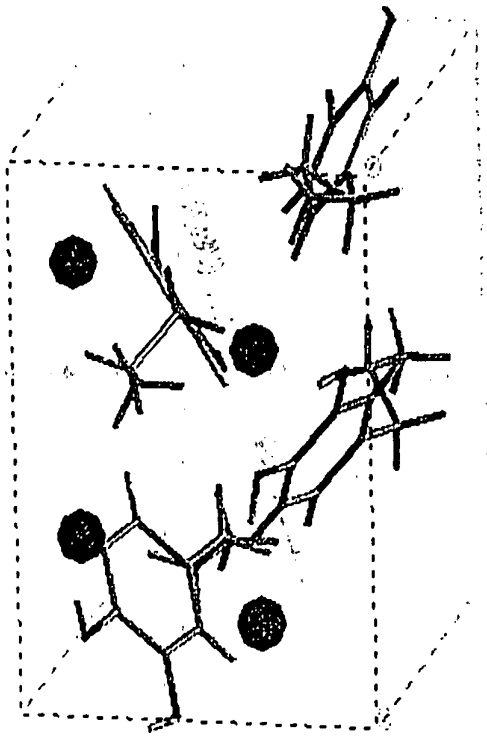


Fig 7c.



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